# Safety Throughout the Life Cycle of Vaccines

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# Disclaimer

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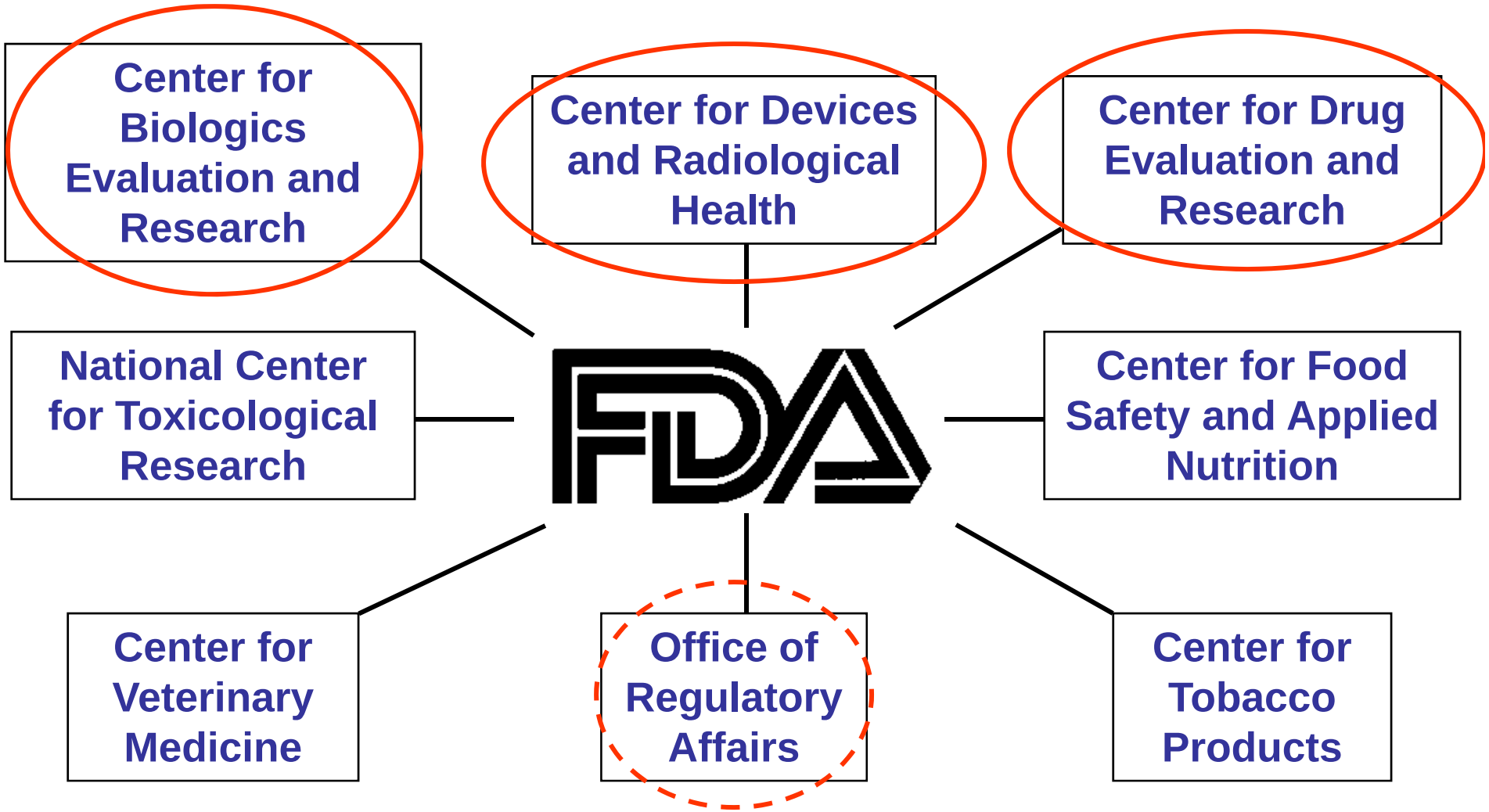
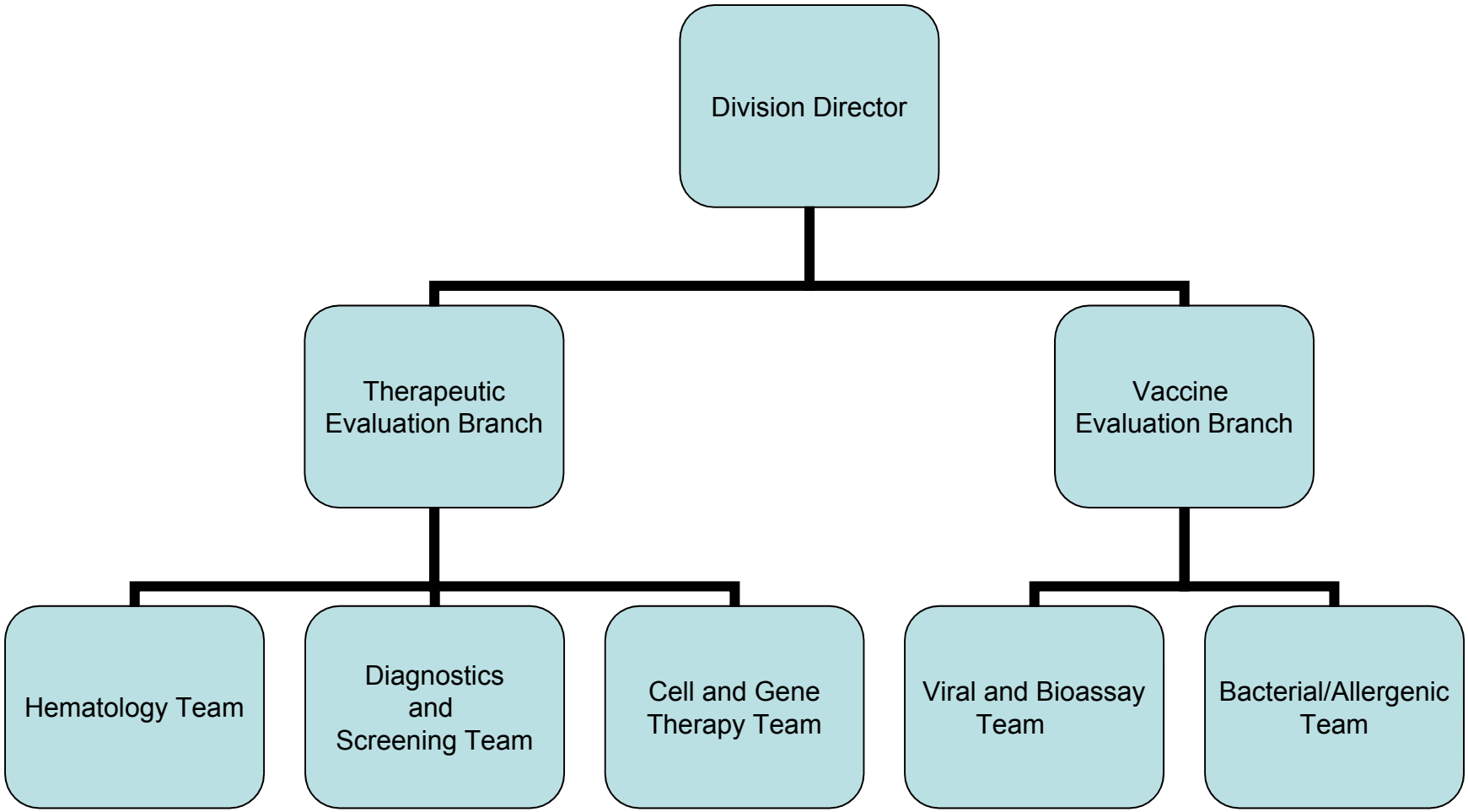
# FDA Organization



# Division of Biostatistics Organizational Chart



# Outline

- Vaccines 101
- Safety in Pre-Market
- Postmarket and SCCS
- Passive Surveillance and VAERS
- Active Surveillance
  VSD, PRISM, Federal Partners
- Open methodological questions
- Conclusions

# Vaccine 101

# Vaccines are not drugs!

- Administered to healthy people
- Designed to prevent disease
- Importance of herd immunity

  Need high buy-in

  Maintaining confidence in vaccines  is key

# Vaccines are not drugs!!

- Like other biologics, vaccines are **licensed**
- FDA: premarket review
- Vaccines in post-market:

  HHS: FDA, CDC, NVPO

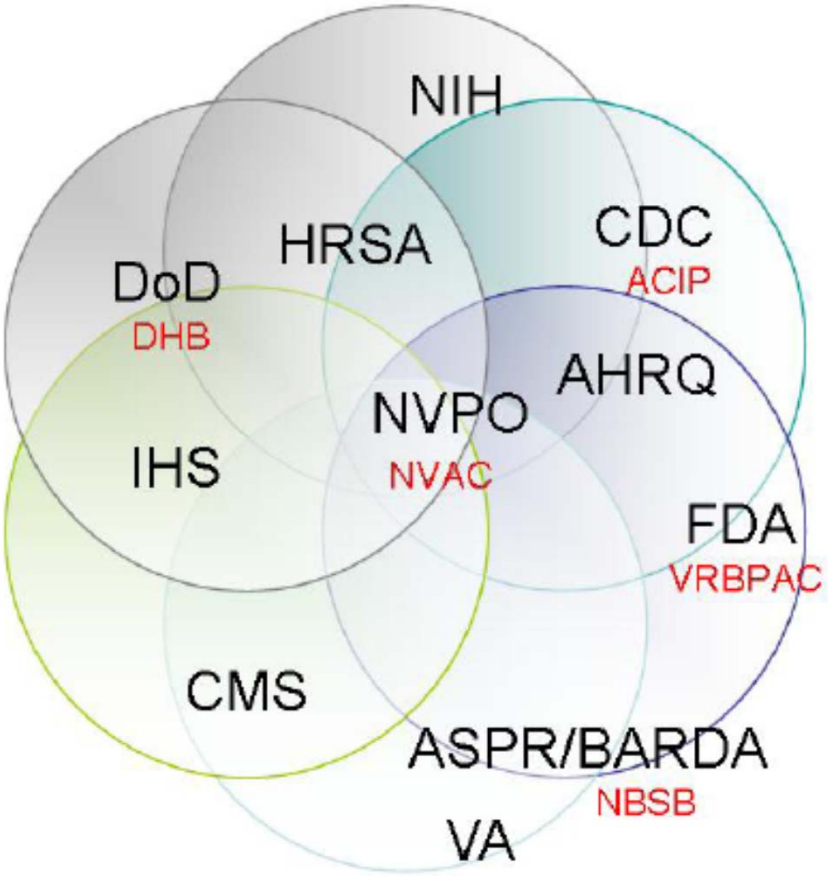
  Global: WHO, EMA, …..
- Pandemic and Seasonal flu Vaccines:

  New variants keep coming
- Lot release review

# Federal Plans to Monitor Immunization Safety for the Pandemic 2009 H1N1 Influenza Vaccination Program

Federal Immunization Safety Task Force

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality
Centers for Disease Control and Prevention
Food and Drug Administration
Health Resources and Services Administration
Indian Health Service
National Institutes of Health
Department of Defense
Department of Veterans Affairs




http://www.flu.gov/professional/federal/fed-plan-to-mon-h1n1-imm-safety.pdf

Advisory Committees in Red

# Immunological Assay

- Required for all vaccines
- Carefully reviewed at FDA
- Immune response endpoint
  - Correlate of protection(?)
    - see papers by Gilbert et al
    - Example: Antibody to HBV
  - Surrogate endpoint (?)
    - see papers by Gilbert or Prentice

# Lot-to-Lot Consistency

- Three lots of vaccine
- Used in a 3 arm study

  ….often sub-study of bigger trial
- Three lots must be comparable

  ….similar to a bioequivalence criteria
- Immunological assay variability can be an issue

  ….Important for design

# Vaccine Development

- Phase 1 Safety studies
- Phase 2 Different doses and schedules
- Hundreds of patients
- Characterize very common A.E.
- Phase 3 Pivotal studies for licensure
- Plan for pharmacovigilance
- Unsafe vaccines don't get to next phase!
- Sometimes additional safety registry

# Efficacy Trials

- First of a kind vaccines:
  Endpoint based on case definition
- Usually has a placebo arm
- Cannot control disease exposure
- Large trials and super-superiority
- VE=Vaccine Efficacy=
  1- (disease rate, V)/(disease rate, C)
- Flu  VE>40% (95% Lower Conf Bound)

# Several trials: common

- Different age classes (e.g. flu)
  - Infants, kids, adults, elderly
- Common concomitant vaccines
- International trials
  - Higher background rates
  - Relevance to US? (e.g. strain types)
- Safety data are captured in all

# Immunogenicity trials

- 2nd of a kind
- Disease prevalence is now lower
- Active control arm
- Non-inferiority of an immune response endpoint (NI Margin: talk with OVRR)
- Multiple serotypes : multiple endpoints

  trivalent flu, Prevnar 13
- Interpretation of safety data ?

# Plan for Pharmacovigilance : During BLA review (DE)

- International Conference on Harmonization (ICH) Guidance for industry: E2E Pharmacogivilance Planning format
- Early consideration of FDAAA 2007 options
- Postmarketing studies are informed by:
  - Experience with post marketing surveillance strengths and limitations
  - Experience with similar products
  - Safety issues identified by Clinical and Statistical reviewers during pre-licensure review

# Vaccines are not drugs !!!

- Some rare but serious events:
  linked to vaccine use
- Guillian Barre Syndrome
  (Swine Flu 1970s)
- Intussusception (Rotavirus 1990s)
- Severe allergic reactions (Vaccines & eggs)

- May trigger additional studies or spur serious post-market surveillance

# Inference for safety in phase 3

- Most studies use 1:1 allocation
- Some expose more to new vaccine
- Flu guidance for established mfg:
  Rule out 1 in 300 adverse event
- Inference with very big N, very small p
  Most articles assume rate>.01 or 1%

# Inference Methods Study: Pre-specified adverse events

- Exact methods:
  - Computationally burdensome in phase 3
  - For safety: symmetric methods
  - 95% confidence interval
  - Want appropriate one sided values
- Score methods are compromise (Newcombe)
- Wald and related methods are poor
- Farrington and Manning for NI not implemented the same across packages.

# Risk difference (RD) or Relative Risk (RR)

- Very rare events, RR exaggerates risk
- RR when control has zero events?
- Deeks et al: RR more stable across studies
- RD provides excess risk estimate

  number of cases per 100,000
- Reporting both makes sense (SPERT, 2009)
- Control of alpha: rarely done if small number of pre-specified events.

# RotaShield

- As of 1998, rotavirus was the most common cause of severe gastroenteritis in infants and children less than 5 y.o. in the U.S.
  - 500,000 physician visits, 50,000 hospitalizations, 20 deaths/year in the U.S.
  - 600,000 deaths/year worldwide
- The first rotavirus vaccine, RotaShield was licensed in August 1998
- RotaShield was voluntarily taken off the market in 1999

# RotaShield and intussusception

- Very soon after licensure, reports of intussusception temporally associated with RotaShield began appearing in VAERS
- Intussusception is a potentially life-threatening bowel obstruction
  - Background incidence in infants ~ 0.0004 cases / year
- Following investigation, CDC determined that 1 – 2 additional cases of intussusception would be caused by RotaShield per 10,000 infant-years

# The REST trial (1)

- Thus, intussusception was a major concern for future rotavirus vaccine candidates
- Development of the RotaTeq vaccine included the Rotavirus Efficacy and Safety Trial (REST)
- ***69,625*** subjects were vaccinated (n=34,837) or placebo (n=34,788)
- The primary efficacy endpoint was based on cases of disease
  - But this was only assessed in 5,673 (8%) of subjects

# The REST trial (2)

- The sample size was driven by the safety endpoint of intussusception
  - Subjects actively monitored for potential intussusception at 7, 14 and 42 days post each dose, then every 6 weeks for 1 year
  - Primary safety win criterion was upper bound of the 95% CI for RR to be ≤ 10 without hitting safety stopping boundaries
  - Group sequential design
    - Initial analysis at n = 60,000
    - Subsequent analyses after each 10,000 subjects up to 100,000
- Study concluded with 6 cases in the vaccine arm, 5 in the placebo arm

# Lessons learned from a huge safety trial

- **A huge trial may only be possible with a relatively easy-to-ascertain primary safety endpoint**
- **Embedding efficacy and detailed safety subsets in the overall safety trial improves efficiency**
  - Always a good idea to collect whatever efficacy and safety information is feasible
- With a background incidence of ~ 1/10,000, even 60,000 – 100,000 subjects will only permit ruling out an RR of 10.
  - Safety trials have to operate within realistic constraints

# Vaccines vs Drugs in Postmarket

# Key differences

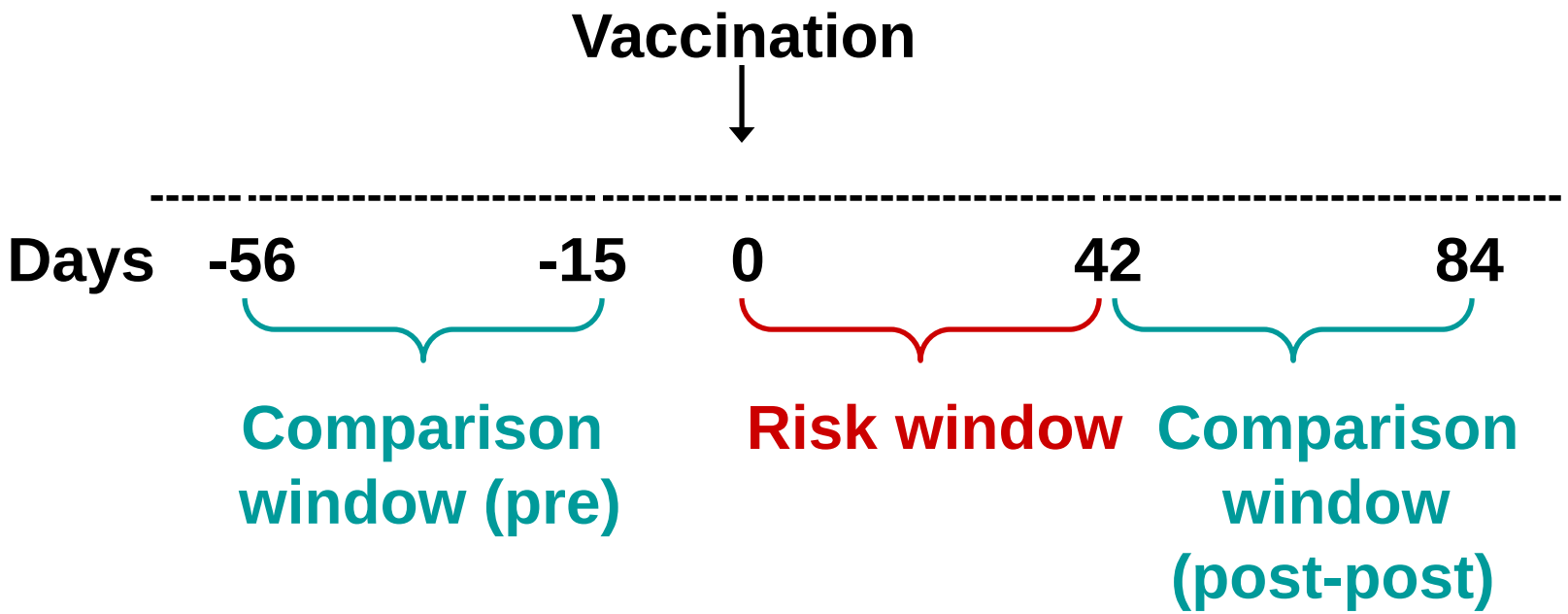
- Fewer possible confounders with vaccines
- Drugs: indications and duration can vary
- Vaccines: limited exposures
- Larger premarket studies imply:

  Looking for very rare A.E.s in postmarket

# Self controlled case series

- Tutorial in Stat in Med (see references)
- Developed methods for vaccine safety
- Each subject serves as own control
- Efficient signal detection
- Doesn't formally address who is at risk
- OMOP methodology comparisons….this can outperform many other methods.

# Self-Controls



# Vaccine Adverse Event Reporting (VAERS)

# Passive Surveillance: VAERS

- Voluntary reports
- Patients, physicians, others
- Most fields are publicly available
- Case of no denominators…

  how many are exposed to product?
- CBER review: Division of Epidemiology
- Use Empirica Signal Detection Software

# Passive Surveillance: AERS and VAERS

- **STRENGTHS:**
  - Open-ended for hypothesis generation
  - Potential detection of new or rare adverse events
  - Timeliness
  - Geographic diversity
  - Capability to monitor production lots
- **LIMITATIONS:**
  - Missing and inaccurate data
  - Under-reporting/Stimulated reporting
  - Absence of controls and denominators
  - Inability to assess causation
  - Low likelihood of detection for long latency events

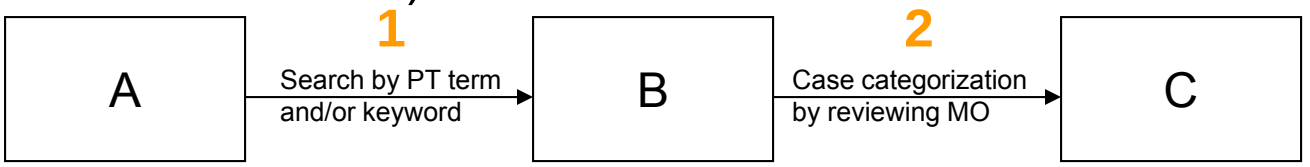
# CBER research initiative

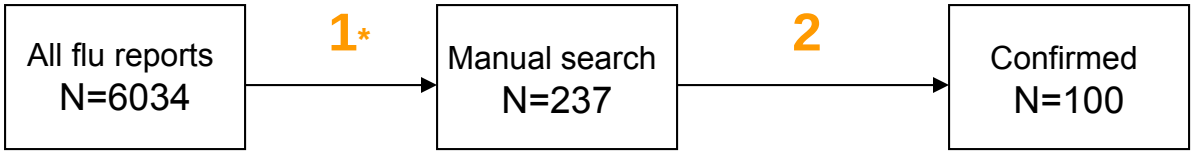
- Text mining of narratives in VAERS
- 2 stage process:
- using natural language processing to extract features from text
- use supervised learning methods to develop classification rule.

**Can evaluation of narratives improve yield rate of anaphylaxis?**

# Review by Medical Officers

- Manual search and review of case reports for H1N1 anaphylaxis (10/12/2009-06/30/2010).




- Important to automate:
  - the whole process, but step 2 requires MO (<=>pdf files) review.
  - at least step 1 and provide MOs with the low number of reports for further review in step 2.

# Training set: Classification Results

| | | MOs' review | | |
|---|---|---|---|---|
| | | Pos | Neg | Totals |
| Text Miner | Pos | 183 | 352 | 535 |
| | Neg | 54 | 5445 | 5499 |
| Totals | | 237 | 5797 | 6034 |

Sensitivity: 77.2%  PPV: 34.2%

Specificity: 94.0%  NPV: 99.0%

# Independent validation

Independent validation of algorithm, truth determined by manual review (N=689):

PPV=30%  NPV=99%

PPV hurt by low prevalence, but NPV suggests text miner can be used to enrich the dataset.

# Vaccine Safety DataLink
# CDC and FDA

# CDC Vaccine Safety Datalink (1991)

- Eight geographically diverse health maintenance organizations that participate in a large linked database representing approximately 3% of U.S. population
- Surveillance and "Hypothesis testing" studies can be conducted
  - Vaccination (exposure)
  - Outpatient, emergency department, hospital and laboratory coding data (health outcomes)
  - Demographic variables (confounders)
  - Accessible medical chart review

# VSD Rapid Cycle Analysis

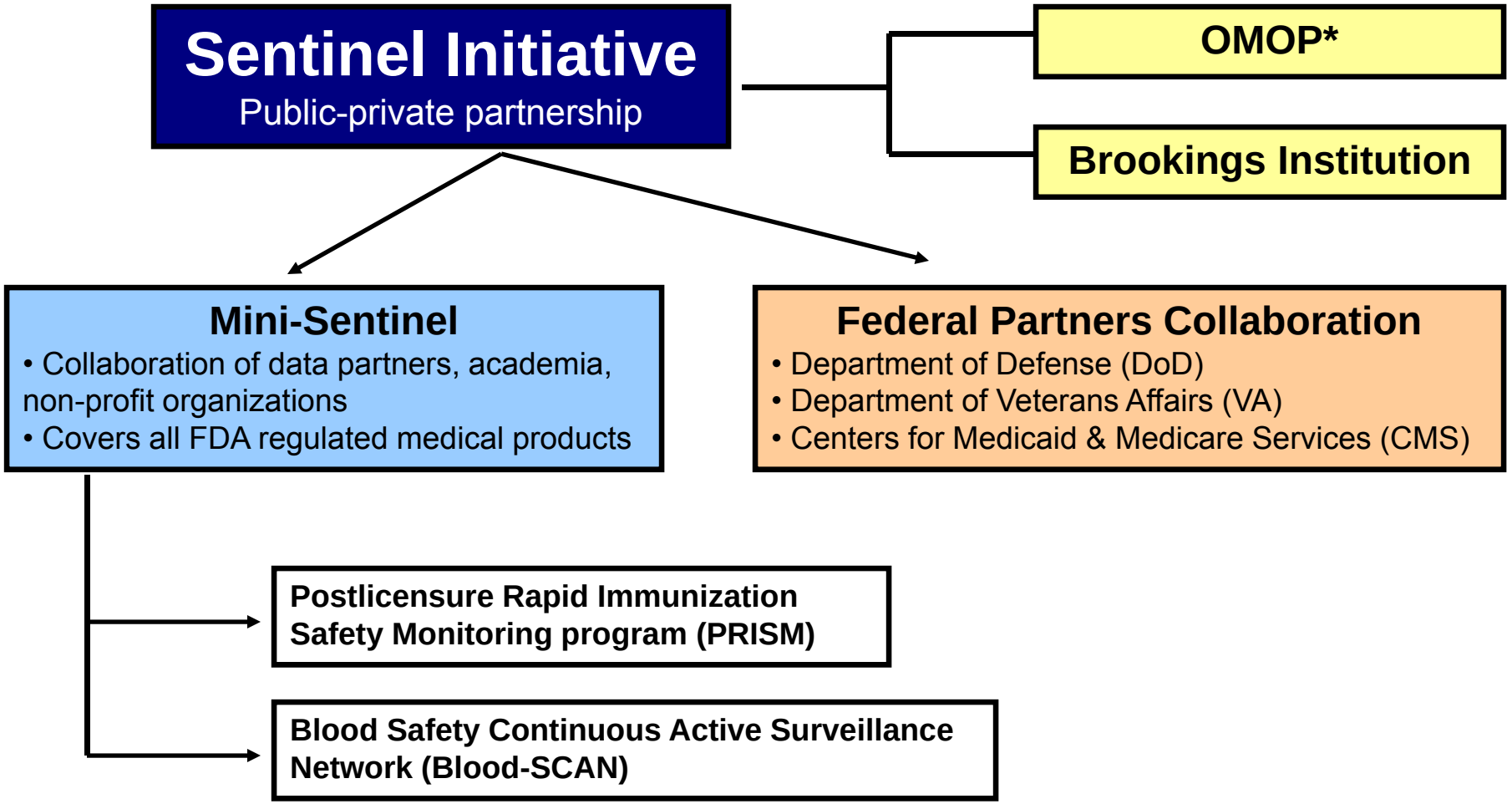
- Method motivated by Wald SPRT:
  Wald: Simple vs Simple Hypotheses
- Near continuous monitoring (weekly)
- Extension to composite alternative
- Two variants:
  Poisson: #events vs expected counts
  Binomial: event rates exposed vs not exp

# Max SPRT
# Kulldorff et al (2011)

- Likelihood ratio statistic
- (Poisson or binomial)

- Length of surveillance fixed (e.g. 2 yrs)
- Time is expected counts not calendar time
- Rapid detection important

# Mini-Sentinel is Part of FDA's Sentinel Initiative




* Observational Medical Outcomes Partnership

# PRISM Basics

- Mini-Sentinel program dedicated to vaccine safety
- Claims based system with data from 4 national health plans
  - Aetna, HealthCore (Wellpoint), Humana, Optum (United Healthcare)
  - Data linked to 8 vaccine registries in USA
- Access to medical records and pharmacy data

Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:291-7.

# Analytic Modular Programs

- Represents next step in standardization
  - From quick query to standardized analytic programs
- Designed to address 2 problems
  - Facilitates simultaneous monitoring of numerous FDA approved medical products
  - Reduces start-up time and resources of customized analyses
- Semi-automated product safety assessments
  - Predefined algorithms to identify exposures, outcomes, comparators
  - Standardized confounding control
  - Analytic choices chosen to cover most scenarios

# Prespecified event: 3 Methods Initially Selected

1. **Self-controlled design**
   - Useful for single or short-term exposures or when no independent comparator group is available
   - When between-person confounding is large but within-person confounding is modest
2. **Exposure match cohort**
   - Uses propensity or disease risk scores in fixed or variable ratio
   - Provides flexible choices of effect measures, multiple endpoints and broad range of alerting rules
3. **Full cohort design with regression**
   - Permits a high degree of analytic flexibility (e.g., the ability to simultaneously evaluate interactions, multiple comparison groups, and subgroups)

# PRISM Methods: Improving Causal Inference

- Improve on design-based confounding control
  - Traditionally use matching (age, site, sex), stratification
  - Limited by number of confounders or high dimensionality
  - Loss of efficiency (cannot use entire cohort)
  - Method like Lunceford and Davidian (2004)

  Group sequential element for surveillance

  See ms by Cook et al (Mini-sentinel site)

# Data Mining Development

- Test whether it is possible to detect adverse events without pre-specifying them a priori
- Develop statistical approach to simultaneously evaluate hundreds of different adverse events
  - Advantage: detect unexpected adverse events
  - Disadvantages: not possible to adjust for all possible confounders, as they vary by disease outcomes

    Finding optimum risk window for all events is hard

    Hierarchy of events imperfect.

Pilot phase: can we detect known signals?

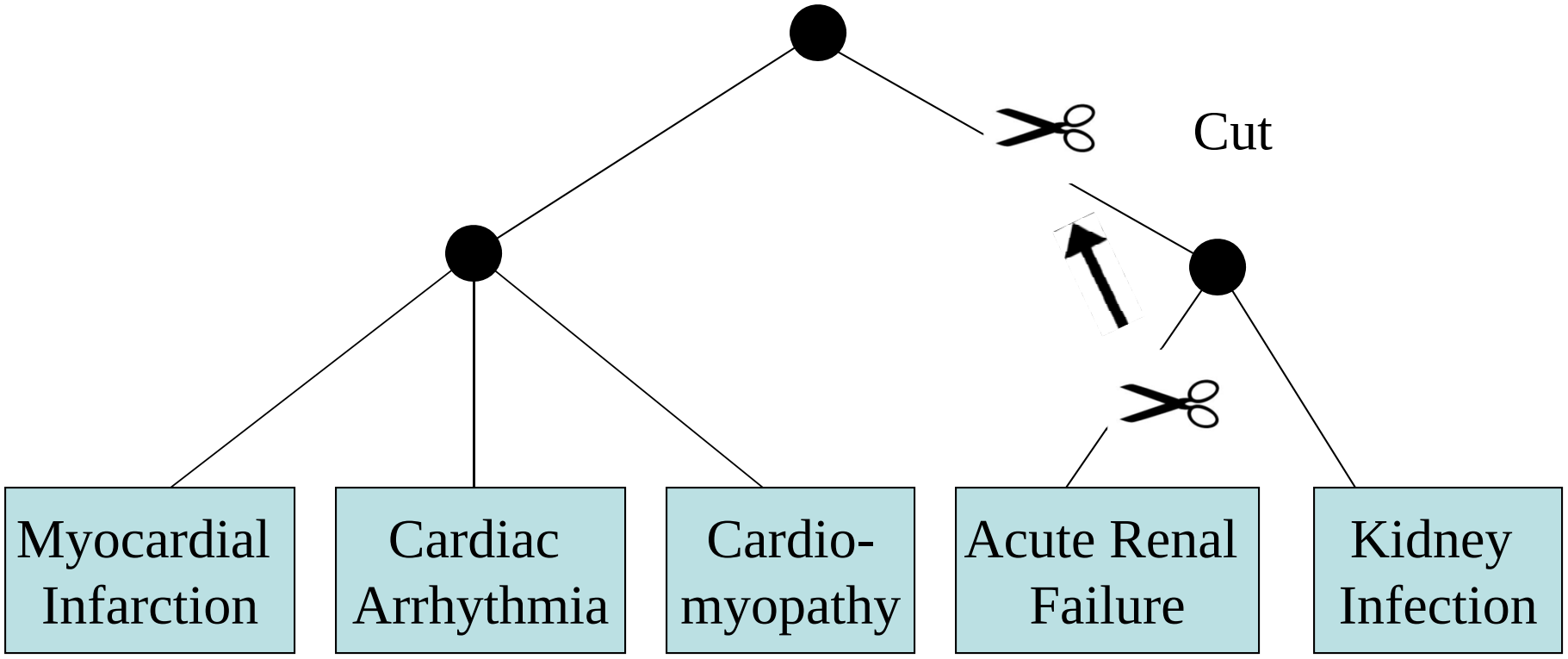
# Mining: 3 Methods Being Evaluated

- Project led by Martin Kulldorff
  - DuMouchel's Gamma Poisson Shrinker
  - Tree-based scan statistic with population based controls
  - Tree-based scan statistic with self-controls

- Basics of Tree Scan algorithm
  - Use a hierarchical tree
  - Evaluate cuts on the tree (assess observed vs. expected at each leaf)
  - Control for multiple testing

Kulldorff M, Fang Z, Walsh S. A tree-based scan statistic for database disease surveillance. Biometrics, 2003,59:323-331.

# Example of a Small Tree



# Tree-based SCAN Statistic

1. Scan the tree by considering all possible cuts on any branch
2. For each cut, calculate the likelihood
3. Denote the cut with the maximum likelihood as the most likely cut (cluster)
4. Generate 9999 Monte Carlo replications under $H_0$.
5. Compare the most likely cut from the real data set with the most likely cuts from the random data sets
6. If the rank of the most likely cut from the real data set is R, then the p-value for that cut is R/(9999+1).

# Tree-based SCAN Statistic

1. Scan the tree by considering all possible cuts on any branch

**Helps answer, "Has FDA observed any new safety issues?" without pre-specifying a particular outcome**

4. Generate 9999 Monte Carlo replications under $H_0$.
5. Compare the most likely cut from the real data set with the most likely cuts from the random data sets
6. If the rank of the most likely cut from the real data set is R, then the p-value for that cut is R/(9999+1).

# Implementation in distributed environment

- Methods assessed
  - Empirical Bayes Gamma Poisson Shrinker (DuMouchel)
  - Tree-based scan statistic (Kulldorff)

  Open challenges:

  Multiplicity of risk windows or age classes

  Constellations of events

  Concomitant vaccines or drugs

# Post-marketing Vaccine Safety Research: Federal Partners

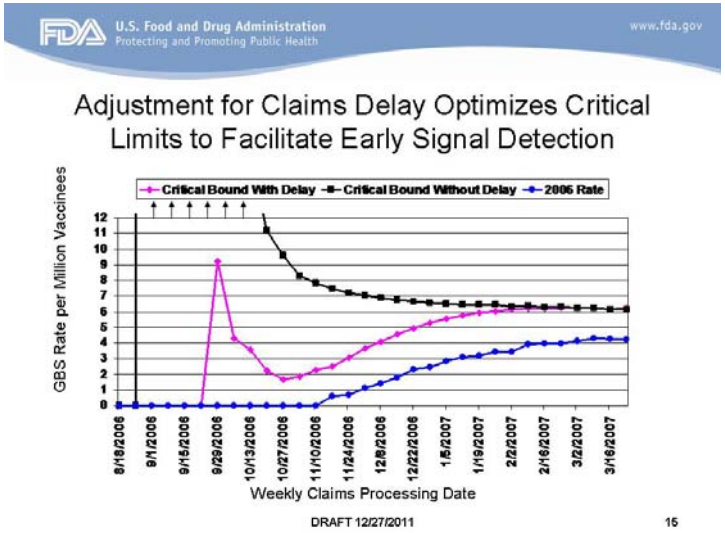
- Claims datasets
  - Near-real time monitoring
  - Centers for Medicare and Medicaid (CMS)
    - Population >35 million
- Comprehensive datasets
  - Electronic data for near-real time monitoring
  - Access to medical records for diagnosis verification and hypothesis confirmation
  - > 1,000,000 beneficiaries in each dataset
    - Indian Health Service
    - Department of Defense
    - Veterans Administration

# A fictional vaccine…..

| | Health Outcome | Action Plan |
|---|---|---|
| **Important Identified Risks** | 1. Anaphylaxis<br>2. Syncope causing injury | • **Quick queries to follow up any safety signals from passive surveillance**<br>• Routine pharmacovigilance |
| **Important Potential Risks** | • Febrile seizures<br>• Immune thrombocytopenic purpura<br>• Myocarditis | • **Prospective sequential surveillance with self controlled analysis**<br>• **Current vs. historical surveillance for rare events**<br>• PMC observational study 50,000 subjects<br>•Routine pharmacovigilance |
| **Important Missing Information** | 1. Safety in pregnant women, older adults (>64 years)<br>2. Unanticipated adverse events | • **Retrospective pregnancy safety study at 3 years postlicensure**<br>• **Data mining**<br>• Routine pharmacovigilance |

# FDA-CMS Project SafeVax: Rapid Assessment of Vaccine Safety

- Developed a novel approach to near real-time safety surveillance adjusting for delay in claims in collaboration with CMS




- 2009–2010 season: monitored safety of seasonal and H1N1 pandemic influenza vaccines
  - Approximately 45 million CMS beneficiaries and more than 3 million H1N1 pandemic vaccinations monitored
- Monitoring of GBS after seasonal influenza vaccine now routine
- More and better data for safety: other adverse events, improved access to medical records, possible exploration of Medicaid data

# FDA Next Steps

- Better integrated safety summaries. Reviewing role critical.
- Data mining in premarket RCTs

  Pediatric vaccines…
- Gaining more hands-on experience with active surveillance datasets.
- Active engagement of DB/DE in best use of Passive Surveillance Data.

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